

The University of Chicago

HYDROGEN-DEUTERIUM EXCHANGE
REACTIONS OF PHENOLS AND
PHENOL ETHERS

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
PHYSICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

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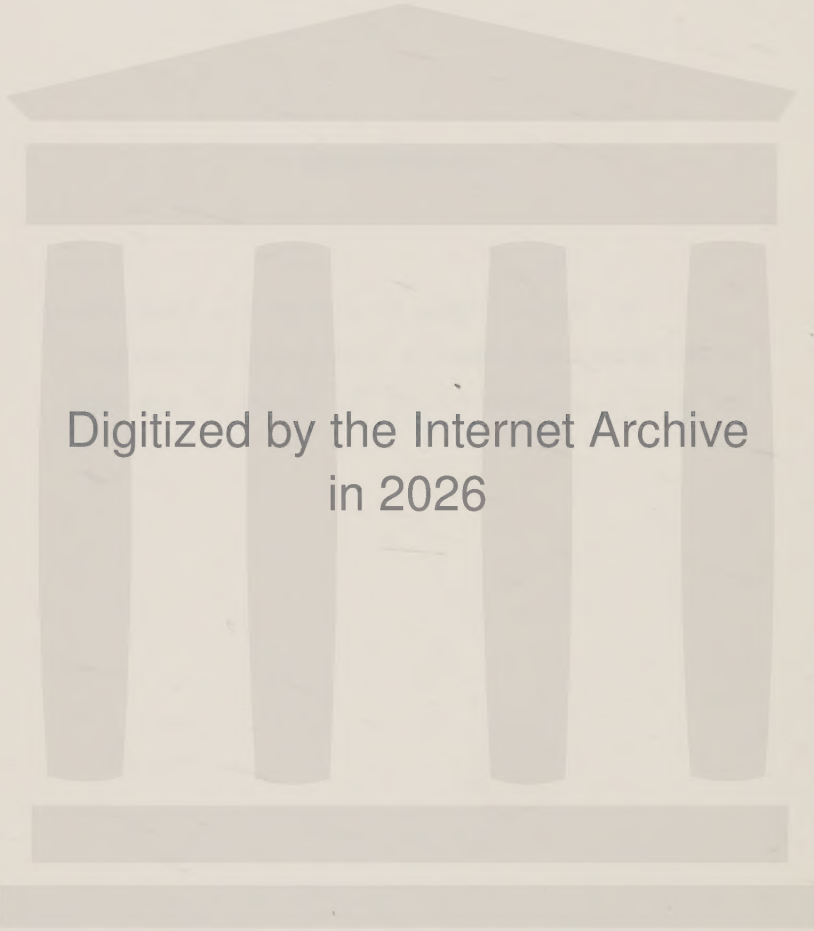
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INTRODUCTION

The chemical behavior of phenols and phenol ethers in nuclear substitution reactions such as nitration, bromination, and coupling is a well known field. In brief, it may be noted that phenols show a greater nuclear substitutive reactivity than do phenol ethers. Within these groups of compounds, the naphthols are more reactive in nuclear substitutions than are the phenols, and the naphthyl ethers react with greater ease in nuclear substitutions than do the phenyl ethers.

In the present research, an isotopic exchange reaction between a phenol or a phenol ether and deuterioethyl alcohol has been used to study the behavior of the nuclear positions of the compound under examination in this type of reaction. An investigation of the relative rates of nuclear hydrogen-deuterium exchange in different aromatic molecules, under comparable conditions, affords an indication of the relative activation energies necessary for substitution of deuterium in the different molecules studied. By substituting deuterium, which is more nearly identical with hydrogen than any other isotope, element, or group, for hydrogen in an aromatic nucleus, the original character of the aromatic molecule is probably so little altered that the further substitution of deuterium will take place essentially as if the subsequent substitution had occurred originally. Thus it is possible to make an almost independent study of a substitutive reactivity of different nuclear positions in an aromatic molecule.

As an example of the conditions under which a nuclear ex-

change reaction is known to take place, Brown, Kharasch, and Sprowls found that in the case of certain substitution derivatives of aniline a small amount of sulfuric acid is required to bring about nuclear deuteration.¹ Since phenols are, in certain respects, similar to aniline, the exchange reactions reported in this paper were in most cases conducted in the presence of a relatively small amount of sulfuric acid. However, since phenols are known to couple in alkaline solution, it was thought of interest to examine the exchange behavior of certain compounds in the presence of a basic catalyst.

As specific examples of phenols and phenol ethers, p-cresol, α - and β -naphthol, anisole, and α - and β -naphthyl alkyl ethers were among those compounds chosen for investigation by means of an acid catalyzed exchange reaction. The possibility of a base catalyzed exchange reaction was investigated with α - and β -naphthyl alkyl ethers, using a relatively small amount of sodium ethylate.

The nuclear reactions of certain phenols, notably 3,4-dimethylphenol, 5-hydroxyhydrindene, and 6-hydroxytetralin, have provided a subject of considerable interest. 3,4-Dimethylphenol and 5-hydroxyhydrindene brominate and couple chiefly in the 6-position. 6-Hydroxytetralin, however, in which the orienting effects might be expected to be similar, brominates and couples mainly in the 5-position. Pointing out that bromination and coupling are reactions typical of enolic systems, Mills and Nixon suggested the hypothesis that, on account of strain factors, the structure of hydrindene would be predominantly that in which a single bond is common to the two rings, while the structure of tetralin would be predominantly that in which a double

¹Brown, Kharasch, and Sprowls, J. Org. Chem., 4 (1939).

bond is common to the two rings.²

Sutton and Pauling, applying the methods of quantum mechanics to the problem, concluded that in hydrindene the favored structure according to the Mills-Nixon hypothesis makes a contribution to the structure of the molecule 1.05 times as great as the other structure. For the case of tetralin, they concluded that the favored structure according to the Mills-Nixon hypothesis makes a contribution 1.04 times as great as the other structure. Sutton and Pauling believe that these differences in contributions of the two Kekulé structures are sufficient to account for the observed differences in reactivity of the nuclear positions in, say, 5-hydroxyhydrindene and 6-hydroxytetralin.³

On the basis of dipole moment data observed with 5,6-dibromohydrindene and the analogous dibromotetralin and dibromoxylene, Sidgwick and Springall have concluded that the suggested favored structure is valid in the case of hydrindene, but that in the case of tetralin the two Kekulé structures contribute equally.⁴

McLeish and Campbell, from a study of the lability of bromine in 6-bromo-7-nitrotetralin and 6-bromo-5-nitrotetralin, find no evidence in favor of Mills and Nixon's suggested favored structure of tetralin.⁵

Kistiakowsky and co-workers argue, from hydrogenation data, that if no so-called fixation exists in the tetralin molecule, no fixation can exist in the hydrindene molecule.⁶

²Mills and Nixon, J. Chem. Soc., 2520 (1930).

³Sutton and Pauling, Trans. Far. Soc., 31, 939 (1935).

⁴Sidgwick and Springall, J. Chem. Soc., 1532 (1936).

⁵McLeish and Campbell, J. Chem. Soc., 1103 (1937).

⁶Kistiakowsky and co-workers, J. Am. Chem. Soc., 59, 830 (1937).

Taylor, in noting that the resonance energies of benzene and hydrindene are identical within the limits of experimental error, pointed out that a fixed Kekulé structure for hydrindene would be impossible.⁷

In the present work, the rate of nuclear hydrogen-deuterium exchange in 3,4-dimethylphenol, 6-hydroxytetralin, and 5-hydroxyhydrindene was examined in order to determine if any difference in reactivities of the two nuclear hydrogens in ortho-position to the hydroxyl group could be detected by this means. As will be brought out in the discussion, it may be possible to determine the relative contributions of individual structures to the actual structure of a given molecule in this manner. For purposes of comparison, a phenol whose two ortho-hydrogens are equivalent, 4-chloro-3,5-dimethylphenol, was studied.

Brown, Kharasch, and Sprowls have found that o-nitrodimethylaniline fails to exchange nuclear hydrogen under conditions which do lead to nuclear exchange in related compounds.¹ In this connection it was thought of interest to examine the exchange reactions of certain ortho-substituted aromatic ethers to see if an analogous behavior could be observed. Accordingly, exchange experiments were performed on the methyl and iso-propyl ethers of α -naphthol and of β -methyl- α -naphthol. Attempts to study the exchange reactions of o-methylanisole and 2,6-dimethylanisole were unsuccessful because of a reaction of these compounds with the ethyl alcohol used as reaction solvent.

EXPERIMENTAL PROCEDURE

The number of exchangeable hydrogen atoms in a given compound was determined by measuring the distribution of deuterium

⁷Taylor, Ann. Reports, 34, 219 (1937).

between ethyl alcohol and the material under investigation. In the present work, this distribution was determined by using deuterio-alcohol of known composition as a solvent and donor of deuterium, and analyzing the recovered deuterio-alcohol for deuterium by the float-temperature method. The experimental procedure and apparatus used for analysis of the deuterio-alcohol, and the calibration data for the quartz float employed, are described by Eberly.⁸

A typical exchange experiment was conducted as follows. A measured sample of the organic compound being investigated was introduced into a reaction tube, the required amount of catalyst was added, and 5 cc. of deuterio-alcohol (0.085 mole) were introduced from a pipette. The tube was then cooled to -80° , sealed to a capillary tube attached to a vacuum line, evacuated to 1 mm. pressure, and sealed off. At the end of the desired reaction time, the tube was opened and the contents were introduced into a 15 cc. distilling flask (neck, 16 mm. in diameter; side-arm, 35 mm. above top of bulb). Sufficient deuterio-alcohol for analysis was distilled off rapidly over a free flame into a test tube (11 x 100 mm.) cooled with a dry-ice bath. The combustion and subsequent analysis of the deuterio-alcohol were carried out as described by Eberly.⁸

CALCULATION OF RESULTS

The number of exchangeable hydrogen atoms in a molecule is calculated on the basis of statistical distribution between the components of a given reaction mixture. If the exchange number at equilibrium is not a whole number, it is assumed that the

⁸Eberly, "Hydrogen-Deuterium Exchange in Ethyl Esters" (Unpublished Ph.D. dissertation, Dept. of Chemistry, University of Chicago, 1938).

partition coefficient for the exchange reaction is different from unity. The equation employed is

$$\text{Exchange number} = \frac{\text{Equivalents of deuterium donor}}{\text{Moles of compound}} \times \frac{\text{Amount of deuterium in compound}}{\text{Amount of deuterium in solvent}}$$

The ratio of deuterium contents may be expressed in any convenient manner. In those cases where an appreciable amount of sulfuric acid was used as catalyst, the deuterium composition of the original deuterio-alcohol was corrected so as to give the composition of the resulting catalytic deuterio-solvent.

In the experiments on the rate of hydrogen-deuterium exchange in certain phenolic compounds, the calculations were performed as follows. The total amount of deuterium in the reaction mixture is mol % EtOD in original alcohol x moles of alcohol (14.77 x 0.085 = 0.01255). The amount of deuterium bound to oxygen in the final reaction mixtures is mol % EtOD in recovered alcohol x total moles of hydroxyl in reaction mixture. The difference between this value and the total moles of deuterium present is equal to the moles of deuterium bound in the nucleus of the compound under investigation. This calculation assumes statistical distribution of deuterium between the ethyl alcohol, the sulfuric acid catalyst, and the hydroxyl group of the organic compound being investigated.

MATERIALS

Deutero-alcohol.--The deutero-alcohol was prepared according to the method of Kharasch, Brown, and McNab.⁹

α-Naphthol.--Eastman Kodak Company.

β-Naphthol.--Sublimed twice in high vacuum, m. p. 121 1/2-

⁹ Kharasch, Brown, and McNab, J. Org. Chem., **2**, 39 (1937).

122 1/2°.

p-Cresol (1).--Kahlbaum p-cresol was distilled in high vacuum. This material contained about 10% of o- and/or m-cresol.

p-Cresol (2).--Eastman Kodak Company (practical grade). This material contained no o- or m-cresol. It was vacuum distilled before use.

α-Naphthyl ethyl ether.--Prepared from α-naphthol and diethyl sulfate, b. p. 271-272°.

β-Naphthyl methyl ether.--Prepared from β-naphthol and dimethyl sulfate. Recrystallized from high-boiling petroleum ether, m. p. 73 1/2°.

β-Naphthyl ethyl ether.--Prepared from β-naphthol and diethyl sulfate. Recrystallized from high-boiling petroleum ether, m. p. 36-37°.

α-Methyl-β-naphthyl ethyl ether.--α-Methyl-β-naphthol (m. p. 109 1/2-110 1/2°) was prepared according to the method of Fries and Hübner,¹⁰ and was ethylated with diethyl sulfate. The ether was recrystallized from high-boiling petroleum ether, m. p. 49-50°.

4-Chloro-3,5-dimethylphenol.--This material was supplied through the courtesy of The Barrett Company and Monsanto Chemical Company. M. p. 113-115° (corr.).

3,4-Dimethylphenol.--Eastman Kodak Company.

5-Hydroxyhydrindene.--Prepared by the rearrangement of phenyl-α-bromopropionate to 5-hydroxyhydrindone, and the reduction of this compound to 5-hydroxyhydrindene.^{2,11} M. p. 53-53 1/2°. For the recrystallization of the crude 5-hydroxyhydrindone water was found to be a more satisfactory solvent than alcohol, which

¹⁰Fries and Hübner, Ber., 39, 439 (1906).

¹¹Auwers and Hilliger, Ber., 49, 2410 (1916).

was used by Auwers and Hilliger.¹¹ After one recrystallization from boiling water, using decolorizing charcoal, the 5-hydroxy-hydrindone melted at 185-186° (corr.).

6-Hydroxytetralin.--Prepared by the sulfonation of tetralin, and the fusion of the crude sodium-6-tetralinsulfonate with alkali. The compound was purified through the 7-sulfonic acid.¹² M. p. 61-61 1/2°.

p-Methylphenetole.--This compound was prepared from p-cresol and diethyl sulfate, b. p. 187-189°.

Anisole.--Eastman Kodak Company.

o-Methylanisole.--Prepared from o-cresol and dimethyl sulfate, b. p. 171 1/2-172 1/2° (corr.).

2,6-Dimethylanisole.--Prepared from 2,6-dimethylphenol and dimethyl sulfate, b. p. 181-182°.

α-Naphthyl methyl ether.--Prepared from α-naphthol and dimethyl sulfate, b. p. 131-132° at 10 mm.

β-Methyl-α-naphthyl methyl ether.--β-Methyl-α-naphthol was prepared by the nitration of β-methylnaphthalene,¹³ and the conversion of the α-nitro compound into the naphthol according to the directions of Lesser.¹⁴ No reference to the methyl ether was found in the literature. To a solution of 7.5 g. of sodium hydroxide (0.18 mole) in 100 cc. of water, 19 g. of steam-distilled β-methyl-α-naphthol (0.12 mole) were added. Then, 23 g. of dimethyl sulfate (0.18 mole) were added, swirling the mixture during the addition. After refluxing the mixture for three hours, a small amount of ether was added, and the top layer was separated and washed with alkali, and with water. After drying over calcium

¹²Schroeter, Ann., 426, 111 (1922).

¹³Vesely and Kapp, Rec. trav. chim., 44, 360 (1925).

¹⁴Lesser, Ann., 402, 38 (1914).

chloride, distillation of the material gave 10 g. of yellowish compound (50% yield); b. p. 129-130° at 9 mm., n_D^{20} 1.6007, d_4^{25} 1.056.

Following the procedure of Heermann,¹⁵ 2 g. of the compound were nitrated in glacial acetic acid solution with concentrated nitric acid. After 12 hours, the separated crystals were filtered by suction and recrystallized from 95% alcohol. The light yellow needles melted at 104-105° (uncorr.). The nitro group is presumably in the 4-position.

Analysis: Calculated for $C_{12}H_{11}O_3N$: N, 6.45. Found: N, 6.82.

α -Naphthyl iso-propyl ether.--No mention of this compound was found in the literature. A solution of sodium methylate was prepared from 4.2 g. of sodium (0.18 mole), 100 cc. of methyl alcohol, and 200 cc. of dioxane. After the addition of 26 g. of technical α -naphthol (0.18 mole), 170 cc. of liquid were distilled off. Then, 34 g. of iso-propyl bromide (0.27 mole) and 2 g. of potassium iodide were added and the mixture was refluxed for six hours. Most of the dioxane was distilled off, water and ether were added, and the layers were separated. The ether layer was washed thoroughly with alkali, and with water. After drying over calcium chloride, distillation of the material gave 7 g. of yellowish compound (21% yield); b. p. 139-140° at 9 mm., n_D^{20} 1.5848, d_4^{25} 1.025.

Two g. of the material were nitrated as described under the previous compound. After 24 hours an oil had separated. The reaction mixture was cooled to -80°, allowed to warm up, and the crystals were filtered by suction. On recrystallization from 70% alcohol, the dark yellow needles melted at 69-70° (uncorr.).

¹⁵Heermann, J. prakt. chem., 44, 238 (1891).

Analysis: Calculated for $C_{13}H_{13}O_3N$: N, 6.06. Found: N, 6.15.

A small amount of the nitro compound was heated for one hour on the steam bath with alcoholic potash. Most of the alcohol was evaporated, the solution was poured into water, and acidified with hydrochloric acid. The precipitate was filtered by suction and recrystallized from water. The light yellow material melted at $163-165^{\circ}$ (uncorr.). The m. p. of 4-nitronaphthol-1 is 166° . The nitro α -naphthyl iso-propyl ether is thus identified as 4-nitro-1-iso-propoxynaphthalene.

β -Methyl- α -naphthyl iso-propyl ether.--Reference to this compound was not found in the literature. A solution of sodium methylate was prepared from 4 g. of sodium (0.17 mole), 100 cc. of methyl alcohol, and 300 cc. of dioxane. Then, 27 g. of steam-distilled β -methyl- α -naphthol (0.17 mole) were added, and 250 cc. of liquid were distilled off through a 25 cm. Vigreux column (to 97°). The hot solution was filtered, cooled to 15° , and the precipitated sodium β -methyl- α -naphthylate was filtered off and washed with two 40 cc. portions of dioxane. The salt was refluxed 14 hours with 150 cc. of dioxane, 32 g. of iso-propyl bromide (0.26 mole), and 2 g. of potassium iodide. Most of the dioxane was distilled off, ether and water were added, and the ether layer was separated and washed thoroughly with alkali, and with water. After drying over calcium chloride, distillation of the material gave 13 g. of yellowish compound (38% yield); b. p. $147-148^{\circ}$ at 12 mm., n_D^{20} 1.5764, d_4^{25} 1.017.

Two g. of the material were nitrated as described previously. After 24 hours, an oily layer had separated. The reaction mixture was chilled to -80° , allowed to warm up, and the crystals were filtered by suction. On recrystallization from 70% alcohol,

the light yellow needles melted at 45-46° (uncorr.). Presumably, the nitro group is in the 4-position.

Analysis: Calculated for $C_{14}H_{15}O_3N$: N, 5.71. Found: N, 5.69.¹⁶

¹⁶The micro-analyses reported in this paper were performed by Dr. T. S. Ma.

TABLE 1
ACID CATALYZED EXCHANGE OF PHENOLS^a

Expt.	Compound	Moles of Compound	Final Mol % D ₂ O	Reaction Time (hours)	Exchange Number	Remarks
79	α -Naphthol	0.00501	2.472	0.25	1.74	...
77	"	0.00651	2.263	0.5	2.67	...
72	"	0.00947	2.054	3.5	2.93	...
68	"	0.00936	2.075	9	2.85	...
62	"	0.00895	2.090	22	2.89	b
65	"	0.00904	2.087	83	2.88	b
58	β -Naphthol	0.01087	2.414	0	1.01	c
78	"	0.00951	2.269	0.25	1.80	...
76	"	0.00945	2.210	0.5	2.10	...
73	"	0.00940	2.231	3.5	2.01	...
61	"	0.00985	2.235	16.5	1.90	...
59	"	0.00986	2.219	51.5	1.97	d
74	p-Cresol (1)	0.00810	2.359	24	1.63	...
60	"	0.00778	2.197	52	2.63	b
69	"	0.00809	2.148	213	2.82	...
70	"	0.00829	2.141	235	2.80	b

^aThe deuterio-alcohol used in these reactions analyzed 2.726 mol % D₂O. In each case approximately 10 mg. of concentrated sulfuric acid was used as catalyst. The reaction temperature was 110 $\pm$ 5 $^{\circ}$. The amount of deuterio-alcohol distilled off for analysis was 3.0-3.5 cc.

^bThe recovered organic compound contained no alkali insoluble material.

^cThe sample was placed in the 15 cc. distilling flask, the deuterio-alcohol was pipetted in, the solution was mixed, and the deuterio-alcohol was distilled off. No sulfuric acid catalyst was used.

^dThe recovered organic compound had an odor of β -naphthyl ethyl ether, and contained a slight amount of alkali insoluble material.

TABLE 2
ACID CATALYZED EXCHANGE OF PHENOL ETHERS^a

Expt.	Compound	Moles of Compound	Final Mol % D ₂ O	Reaction Time (hours)	Exchange Number	Remarks
63	α -Naphthyl ethyl ether ^b	0.00921	2.673	22	0.18	d
66	"	0.00921	2.353	83	1.46	d
71	"	0.00921	2.298	119	1.72	...
67	"	0.00921	2.263	206	1.89	...
51	β -Naphthyl methyl ether ^c	0.01031	2.572	24	0.49	e
53	"	0.00897	2.485	112	0.92	e
52	"	0.00897	2.465	190	1.00	e
55	"	0.00903	2.472	410	0.97	e
56	α -Methyl- β -naphthyl ethyl ether ^c	0.00373	2.722	142	0.03	d

^aThe deutero-alcohol used in these reactions analyzed 2.726 mol % D₂O. In each case approximately 10 mg. of concentrated sulfuric acid was used as catalyst. The reaction temperature was $110^{\circ} \pm 5^{\circ}$.

^bThe amount of deutero-alcohol distilled off for analysis was 3.0-3.5 cc.

^cThe deutero-alcohol was recovered from the reaction mixtures by complete distillation from the reaction tubes on the vacuum line, and subsequent complete redistillation in vacuum.

^dThe recovered organic compound contained no alkali soluble material.

^eThe redistilled deutero-alcohol had a slight odor of the organic compound.

TABLE 3

BASE CATALYZED EXCHANGE OF PHENOL ETHERS^a

Expt.	Compound	Moles of Compound	Final Mol % D ₂ O	Reaction Time (hours)	Exchange Number	Remarks
80	α -Naphthyl ethyl ether	0.00921	2.740	4	0.00	...
81	"	0.00921	2.733	94	0.00	b
82	"	0.00921	2.737	284	0.00	b
83	β -Naphthyl ethyl ether	0.00908	2.726	94	0.00	b
84	"	0.00908	2.758	284	0.00	b

^aThe deuterio-alcohol used in these reactions analyzed 2.726 mol % D₂O. In each case approximately 45 mg. of sodium were used as catalyst. The reaction temperature was 110°±5°. The amount of deuterio-alcohol distilled off for analysis was 3.0-3.5 cc.

^bThe recovered organic compound contained no alkali soluble material.

TABLE 4

RATE OF EXCHANGE OF 4-CHLORO-3,5-DIMETHYLPHENOL

Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium	Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium
175	13.26	0	0	178	12.52	60.5	0.00075
172	13.13	6	0.00017	179	12.22	100	0.00103
182	12.98	13	0.00033	181	11.95	142	0.00128
174	12.89	20	0.00041	177	11.81	216	0.00143
173	12.76	30	0.00053	183	11.72	265	0.00150
176	12.68	40	0.00061	180	11.64	342	0.00157

TABLE 5

RATE OF EXCHANGE OF 3,4-DIMETHYLPHENOL

Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium	Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium
104	13.24	0	0	95	11.80	25	0.00143
105	13.22	0	0	94	11.81	30	0.00143
113	13.16	1	0.00015	107	11.69	34	0.00154
96	12.96	3	0.00035	106	11.68	40	0.00155
93	12.61	5	0.00066	112	11.72	45	0.00151
110	12.50	9.5	0.00077	102	11.52	45	0.00168
103	12.20	15	0.00105	99	11.52	120	0.00168
97	11.95	20	0.00128	100	11.53	140	0.00167

TABLE 6

RATE OF EXCHANGE OF 6-HYDROXYTETRALIN

Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium	Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium
142	13.22	0	0	147	11.79	30	0.00145
136	13.07	1	0.00025	154	11.74	35	0.00149
137	12.83	3	0.00045	145	11.76	40	0.00147
143	12.65	5	0.00063	148	11.67	45	0.00156
153	12.20	10	0.00105	149	11.65	50	0.00157
139	12.04	15	0.00120	146	11.64	60	0.00158
140	11.93	20	0.00131	135	11.55	180	0.00167
141	11.92	25	0.00133	134	11.55	200	0.00167

TABLE 7
RATE OF EXCHANGE OF 5-HYDROXYHYDRINDENE

Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium	Expt.	Final Mol % EtOD	Reaction Time (hours)	Moles Nuclear Deuterium
122	13.22	0	0	132	11.95	30	0.00128
123	13.30	0	0	131	11.92	35	0.00132
130	13.10	1	0.00021	128	11.80	40	0.00143
117	12.86	3	0.00044	124	11.78	45	0.00145
116	12.65	5	0.00063	125	11.72	50	0.00150
120	12.34	10	0.00093	133	11.71	55	0.00152
118	12.20	15	0.00105	126	11.59	90	0.00164
119	12.10	20	0.00115	127	11.55	140	0.00166
121	11.99	25	0.00125				

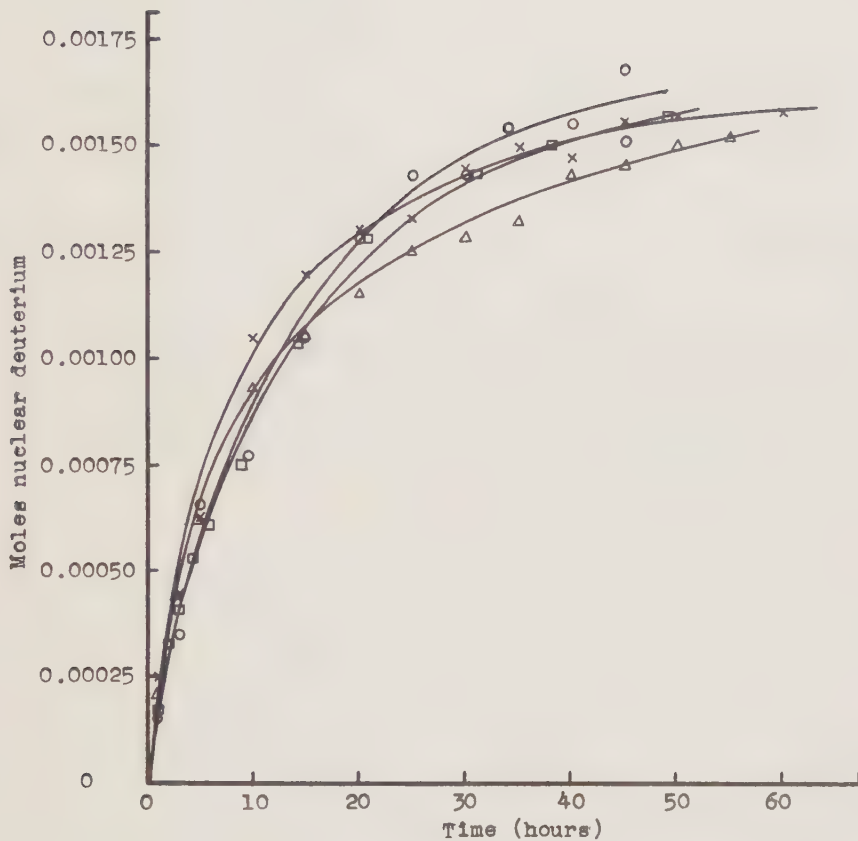


Figure 1.-- Rate of exchange of 4-chloro-3,5-dimethylphenol (□), 3,4-dimethylphenol (○), 6-hydroxytetralin (×), and 5-hydroxyhydrindene (Δ).

TABLE 8
SUPPLEMENT TO TABLES 4, 5, 6, AND 7

Compound	Expt.	Hydroxyl Exchange Number	Expt.	Nuclear Exchange Number ^a
4-Chloro-3,5-dimethylphenol	175	1.06	180	1.65
3,4-Dimethylphenol	104	1.08	99	1.78
	105	1.10	100	1.77
6-Hydroxytetralin	142	1.10	135	1.77
			134	1.77
5-Hydroxyhydrindene	122	1.10	126	1.73
	123	1.03	127	1.76

^aCalculated on the basis of statistical distribution of deuterium between the ethyl alcohol, the catalyst, and the hydroxyl group of the phenol.

APPENDIX TO TABLES 4, 5, 6, AND 7

The reaction solvent was prepared by adding 2.57 cc. of concentrated sulfuric acid to 450 cc. of deuterio-alcohol (approximately 50 mg. of sulfuric acid, 0.001 equivalent, per 5 cc. of deuterio-alcohol). The original composition of the deuterio-alcohol was 14.77 mol % EtOD. Corrected for the dilution effect of the catalyst added, this value becomes 14.60 mol % EtOD. Preliminary experiments showed that within a few minutes at 60° the sulfuric acid was half esterified to ethyl hydrogen sulfate. It was also found that at 60°, no detectable amount of diethyl sulfate was formed within a time of eight days. However, at the time the experiments reported in Table 4 were performed, 100 days after the catalytic deuterio-alcohol was made up, it was found that only 0.0003 equivalent of acid was present in 5 cc. of the catalytic

solvent, compared to 0.0005 equivalent of ethyl hydrogen sulfate originally present.

The experiments carried out at "zero" time were performed as follows. The sample was placed in the 15 cc. distilling flask, the catalytic deuterio-alcohol was pipetted in, and after mixing the solution the deuterio-alcohol was distilled off. In the other experiments, the weighed sample was introduced into the reaction tube and 5 cc. of the catalytic deuterio-alcohol (0.086 mole of hydroxyl hydrogen) were introduced by pipette. The reaction tubes were placed in a thermostat at 60.0°. The amount of deuterio-alcohol distilled off for analysis was approximately 1.5-2.0 cc.

The amounts of compound used were: 4-chloro-3,5-dimethylphenol, 0.00818 mole; 3,4-dimethylphenol, 0.00818 mole; 6-hydroxytetralin, 0.00816 mole; 5-hydroxyhydrindene, 0.00819 mole.

TABLE 9
ACID CATALYZED EXCHANGE OF α -NAPHTHYL ETHERS^a

Expt.	Compound	Final Mol % D ₂ O	Reaction Time (hours)	Exchange Number
166	α -Naphthyl methyl ether	2.115	238	1.15
165	β -Methyl- α -naphthyl methyl ether	2.404	238	0.08
169	α -Naphthyl iso-propyl ether	2.108	213	1.18
168	β -Methyl- α -naphthyl iso-propyl ether	2.407	213	0.07

^aThe reaction temperature was 60.0°. The composition of the deuterio-alcohol used in these reactions was 2.456 mol % D₂O. Corrected for the dilution effect of the catalyst employed (55 mg. of concentrated sulfuric acid) the composition becomes 2.427 mol % D₂O. The amount of compound used was 0.0110 mole. The amount of deuterio-alcohol distilled off for analysis was 2 cc. In each case, a slight odor of the naphthyl ether was detected after evaporating a drop of the deuterio-alcohol distilled for analysis.

TABLE 10
MISCELLANEOUS EXCHANGE EXPERIMENTS ^a

Expt.	Compound	Moles of Compound	Final Mol % EtOD	Reaction Time (hours)	Exchange Number
155	p-Cresol (2) ^b	0.0082	13.30	0	1.02
156	"	0.0082	13.20	15	1.11
157	"	0.0082	13.16	20	1.15
108	Anisole ^c	0.0077	14.21	88	0.3
150	"	0.0116	11.64	68	1.9
151	α -Naphthyl methyl ether ^d	0.0160	13.69	70	0.36

^aThe deuterio-alcohol used was the catalytic deuterio-alcohol used in the rate of exchange experiments (14.60 mol % EtOD). The reaction temperature was 60.0°, except in experiment 150, where it was 110°±5°.

^bExperiment 155, at "zero" time, was performed as described previously. In each case, 1.5-2.5 cc. of deuterio-alcohol were distilled off for analysis.

^cAt the end of the reaction, approximately 3 cc. of deuterio-alcohol were distilled off. This was redistilled, taking about 1.5 cc. for analysis. In each case, the redistilled deuterio-alcohol had an odor of anisole.

^dApproximately 1.5 cc. of deuterio-alcohol were distilled off for analysis.

TABLE 11

EXCHANGE EXPERIMENTS IN WHICH DECOMPOSITION OF
THE ORGANIC COMPOUND WAS OBSERVED^a

Expt.	Compound	Catalyst	Time (hrs.)	Remarks
40	p-Methyl-phenetole	neutral	61	Considerable diethyl ether was formed. The residual organic compound gave a strong coloration with ferric chloride solution.
163	2,6-Dimethyl-anisole	55 mg. H_2SO_4	63	A diethyl ether-like odor was detected in the recovered alcohol. The residual organic compound contained about 50 mg. of alkali soluble material.
162	o-Methyl-anisole	55 mg. H_2SO_4	63	A diethyl ether-like odor was detected in the recovered alcohol. The residual organic compound contained about 20 mg. of alkali soluble material.
164	o-Methyl-anisole	20 mg. H_2SO_4	20	The residual organic compound contained a small amount of alkali soluble material.

^aApproximately 0.01 mole of compound was used. The reaction temperature was $110^{\circ}\pm 5^{\circ}$.

DISCUSSION

In previous similar studies of nuclear acid catalyzed exchange reactions of aromatic compounds,^{1,9} it has been found that the number of exchangeable positions agrees closely with the total number of positions which are ordinarily substitutable in such reactions as nitration, sulfonation, and halogenation. Thus it appears that the nuclear positions which undergo the exchange reaction are the same as those which undergo the ordinary substitution reactions. A theory of nuclear substitution has been pro-

posed which is based on the interpretation of the structure of aromatic molecules as resonance hybrids.¹⁷ Brown, Kharasch, and Sprowls, using a similar interpretation, believe that the nuclear exchange reaction of various substitution derivatives of aniline proceeds through a zwitterion resonance structure.¹ In analogy to the proposal of these authors, it is believed that nuclear hydrogen-deuterium exchange in phenols and phenol ethers proceeds as follows.



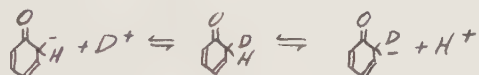
The function of the sulfuric acid in promoting nuclear exchange is believed to lie in its comparatively great deutron donative tendency.

In this research it was found that the number of exchangeable nuclear hydrogens in the compounds investigated approached closely the number of nuclear hydrogens which are reactive in the ordinary substitution reactions. Thus it was found that α -naphthol and its ethyl ether each exchanged 1.9 nuclear hydrogens, presumably the 2- and 4-hydrogens, and that β -naphthol and its methyl ether each exchanged 0.9 nuclear hydrogen, presumably the α -. p-Cresol and 3,4-dimethylphenol, for example, were found to each exchange 1.8 nuclear hydrogens, presumably the o-hydrogens. Thus from the experimental data it appears that the partition coefficients in the nuclear hydrogen-deuterium exchange reactions studied are such that the exchange numbers, calculated assuming statistical distribution, fall somewhat below whole numbers. The calculated exchange numbers for the hydroxyl group in the cases

¹⁷For a brief discussion of this theory see Gilman, "Organic Chemistry," John Wiley and Sons, 1938, pp. 1881-1885.

studied fell between 1.01 and 1.10.

In comparison with the fact that phenols are known to couple more readily than phenol ethers,¹⁸ it was found that the phenols exchanged nuclear hydrogen approximately 10 to 100 times as rapidly as the phenol ethers. This wide variation in rates of exchange is believed to be due to the fact that in the case of the phenols, an appreciable concentration of the phenolate anion exists in the reaction mixture. The mechanism of the exchange reaction of phenols is postulated as proceeding through the nuclear resonance structures of the anion. For instance



Since no separation of formal charges is involved in writing the nuclear resonance structures of a phenolate anion, as is the case in writing the zwitterion resonance structures of a phenol ether, $\text{C}_6\text{H}_5\text{OR}^+$, it is believed that the nuclear resonance structure of a phenolate anion will be a form of lower energy content than the zwitterion resonance structure of a phenol ether, and that the activation energy for the exchange of a phenol will be lower, and the exchange reaction faster, than in the case of a phenol ether.

Orton and Everatt have found that α -naphthol couples more readily than does phenol.¹⁹ In comparison with this fact, it was found that α - and β -naphthol exchanged nuclear hydrogen about 100 times as fast as p-cresol. The explanation for this variation in rate of exchange is believed to lie in the differences in the structures of the naphthalene and benzene nuclei. In the case of naphthalene, the structure  makes a contribution to the

¹⁸Meyer, Ann., 398, 74 (1913).

¹⁹Orton and Everatt, J. Chem. Soc., 93, 1012 (1908).

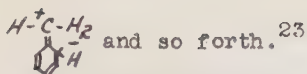
structure of the molecule 1.14 times as great as either of the structures  and .²⁰ Therefore, for the naphthols, the structures  and  make a contribution at least 1.14 times as great as the structures  and . However, in benzene the structures  and  make an equal contribution, as do the two structures  and  in a symmetrical phenol. It seems not unreasonable to assume that the energy of activation for hydrogen-deuterium exchange through a given nuclear resonance structure will depend on the relative contribution of the canonical structure from which the nuclear resonance structure is derived. Thus the activation energy for the exchange of a naphthol, where the structures  make the largest contribution, will presumably be less than that for a phenol, where the structures  and  make equal contributions, and in consequence the nuclear exchange reaction will be more rapid.

The activating effect which a methyl group is known to exert on ortho- and para-positions is apparent on comparing the rate of exchange of p-cresol and 3,4-dimethylphenol. The latter compound exchanges nuclear hydrogen twenty times as rapidly as the former. It is possible that the effect known as hyperconjugation²¹ is responsible for the activating influence of a methyl group. According to this interpretation, we may write, for example, toluene as . The enhanced rate of nuclear substitution of this molecule, which, for instance, undergoes nitration fourteen times as fast as benzene,²² is believed to occur through the nuclear resonance structures of this hyperconjugated system,

²⁰Pauling and Wheland, *J. Chem. Phys.*, **1**, 362 (1933).

²¹Mulliken, *J. Chem. Phys.*, **7**, 339 (1939).

²²Wibaut, *Rec. trav. chim.*, **34**, 241 (1915).



In similarity to the comparative rates of exchange of the naphthols and p-cresol, it was found that α -naphthyl methyl ether exchanged hydrogen at least twice as fast as anisole. In this connection, it may be noted that α -naphthyl methyl ether couples more easily than anisole.²⁴ As before, the difference in rate of nuclear exchange is ascribed to the fact that in α -naphthyl methyl ether the structures make the largest contribution to the actual structure of the molecule, while in anisole the two structures and contribute equally.

Under vigorous conditions, the 3-position in certain naphthalene derivatives may be substituted.²⁵ However, since the structures from which the active zwitterion resonance structures are derived make a comparatively small contribution,²⁰ these zwitterion resonance structures would be expected to be structures of relatively high energy content. In consequence, the activation energy for the exchange process would be relatively high, and the rate of exchange slow. Actually it was found that under the reaction conditions employed the necessary energy of activation was not attainable, for β -naphthyl methyl ether exchanged only one hydrogen, even after 17 days reaction at 110° , and α -methyl- β -naphthyl ethyl ether did not exhibit any exchange after six days reaction at 110° .

In an attempt to induce nuclear hydrogen-deuterium exchange in the naphthyl alkyl ethers by the use of a relatively

²³This interpretation was suggested by Dr. W. G. Brown.

²⁴Meyer, Irschick, and Schlösser, Ber., 47, 1741 (1914).

²⁵Bromination; Fries and Hübner, Ber., 39, 443 (1906).

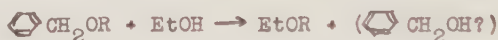
Carbonation; Schmitt and Burkard, Ber., 20, 2702 (1887).

small amount of sodium ethylate, it was found that neither α -naphthyl ethyl ether nor β -naphthyl methyl ether exchanged hydrogen even after twelve days reaction at 110° . Apparently, then, sodium ethylate is not a strong enough base to enable these compounds to exchange nuclear hydrogen by functioning as acids.

In examining the exchange reaction of p-methylphenetole it was found that this compound reacted with the ethyl alcohol to give p-cresol and diethyl ether.



Similarly, in investigating the exchange reactions of o-methylanisole and 2,6-dimethylanisole it was found that these compounds reacted with the ethyl alcohol to form the phenol and methyl ethyl ether. The only mention of this type of reaction found in the literature is the observation of Oda,²⁶ who found that benzyl ethyl ether and benzyl propyl ether reacted with ethyl alcohol to form diethyl ether and ethyl propyl ether, respectively, and presumably benzyl alcohol.



An inhibition of the nuclear exchange reaction, apparently similar to that observed by Brown, Kharasch, and Sprowls in the case of o-nitrodimethylaniline,¹ has been met with in a β -methyl- α -naphthyl ether. The exchange behavior of the following two pairs of compounds was investigated.



I



II

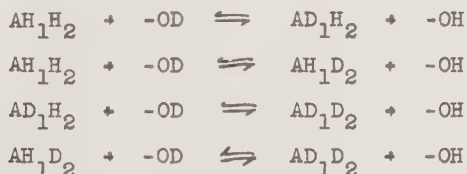
Pair I, with a CH group of the adjacent ring in one ortho-position to the ether group, was found to exchange readily. Pair II, how-

²⁶Oda, J. Soc. Chem. Ind. Japan, 36, 334 (1933).

ever, with a CH group of the adjacent ring in one ortho-position and a CH₃ group in the other ortho-position, was found to exhibit no exchange.

The classical structural theory requires that in the zwitterion resonance structures,  and so forth, through which exchange is believed to take place, the alkyl group attached to oxygen be in the plane of the ring. It is believed that in the compounds of Pair II, the ortho-groups tend to prevent the ether group from lying in the plane of the ring; in other words, the energy content of the molecules whose ether group does lie in the plane of the ring will be higher than that of those whose ether groups are out of the plane of the ring. This means that the zwitterion resonance structures of Pair II will make a smaller contribution to the structure of the molecule than do those of Pair I, and that the activation energy for the exchange reaction will be higher for the compounds of Pair II than that for the compounds of Pair I. In order to inhibit the exchange reaction under the experimental conditions employed, the increased activation energy need not be more than some 5,000-10,000 cal. Thus the energy of rotation of the ether group in an otherwise suitable compound need not be sufficient to cause optical isomerism.

In connection with the rate of exchange experiments with 4-chloro-3,5-dimethylphenol, 3,4-dimethylphenol, 6-hydroxytetralin, and 5-hydroxyhydrindene, it may be noted that the following reactions are involved. The two nuclear hydrogens ortho to the hydroxyl group are marked 1 and 2.



No mathematical solution of the kinetic problem involved has been attempted. However, a rough comparison between the rates of exchange of the two hydrogens ortho to the hydroxyl group in each of the compounds was made as indicated in the following table.

TABLE 12
RELATIVE RATES OF EXCHANGE OF ORTHO-HYDROGENS

Compound	Time in Hours of Nuclear Exchange from 12.5% to 37.5% of Completion	Time in Hours of Nuclear Exchange from 62.5% to 87.5% of Completion	Ratio
4-chloro-3,5-dimethylphenol	31	110	3.5
3,4-dimethylphenol	5	16	3.2
6-hydroxytetralin	3.5	21	6
5-hydroxyhydrindene	4	30	7.5

In 4-chloro-3,5-dimethylphenol, where the two hydrogens ortho to the hydroxyl group are equivalent, the rate ratio is 3.5. The fact that this ratio is not unity is no doubt attributable to concentration changes in the exchange reaction mixtures. 3,4-Dimethylphenol, which is more reactive in bromination and coupling in the 6-position, shows a rate ratio which is almost the same as that of 4-chloro-3,5-dimethylphenol. Apparently, then, the two ortho-hydrogens in 3,4-dimethylphenol are equivalent in so far as hydrogen-deuterium exchange is concerned. 6-Hydroxytetralin shows a rate ratio of 6. In view of the greater bromination and coupling reactivity of the 5-position, it seems likely that it is the 5-hydrogen which is exchanging more rapidly than the 7-hydrogen. Then, in view of the fact that a contributing structure , derivable from a structure , is believed necessary to

nuclear exchange, it seems probable that the structure  makes the greatest contribution to the actual structure of the tetralin molecule, in harmony with the conclusions of Mills and Nixon. In a similar manner, if it is the 6-hydrogen in 5-hydroxyhydrindene which is exchanging more rapidly than the 4-hydrogen, it seems likely that the structure which makes the greatest contribution to the hydrindene molecule is , in accordance with the Mills-Nixon hypothesis.

The evidence of Sidgwick and Springall,⁴ who found that the  moment in 6,7-dibromotetralin was the same as that in 4,5-dibromo-o-xylene, may be invalid due to the fact that possible interaction between the bromine atoms may overshadow an effect on the  moment of the postulated favored structure.

The observation of McLeish and Campbell,⁵ who found that 5-nitro-6-bromotetralin does not react with piperidine, might not necessarily point to their conclusion that the favored structure  is ruled out, because of possible steric interaction between the nitro group and the adjacent CH₂ group of the saturated ring.

In regard to the conclusions of Taylor,⁷ it may be said that the magnitude of the effect on the resonance energy of hydrindene of small differences in the contributions of the two Kekulé structures is no doubt a matter open to question.

SUMMARY

Phenols exchange nuclear hydrogen more rapidly than do phenol ethers. This difference in rates of exchange is believed to be due to the presence of phenolate anions in an exchange reaction mixture of a phenol.

Naphthols exchange nuclear hydrogen faster than phenols,

and naphthyl ethers exchange nuclear hydrogen faster than phenyl ethers. This difference is believed to be due to the relatively large contribution of the structure  to the actual structure of naphthols and naphthyl ethers.

Hyperconjugation is suggested as the property responsible for the activating influence of a methyl group.

The 3-position in a naphthyl ether does not exhibit exchange. This is believed to be due to the relatively small contribution to the structure of the molecule of the structures  and  .

Naphthyl alkyl ethers are unable to exchange nuclear hydrogen by functioning as acids.

Certain phenyl ethers were found to undergo alcoholysis.



An inhibition of the nuclear exchange reaction has been observed in the methyl and iso-propyl ethers of β -methyl- α -naphthol.

Rate of exchange evidence is believed to point to the conclusion that the favored structures of hydrindene and tetralin according to the Mills-Nixon hypothesis are valid.

